

To Replace or Not to Replace: Nutritional Vitamin D in Dialysis.

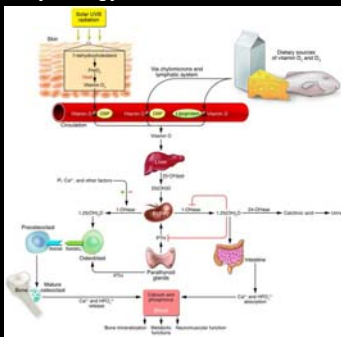
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Objectives

- Review Vitamin D Physiology
- Review Current Replacement Guidelines in CKD and ESRD
- Discuss the available evidence regarding replacement in pts with ESRD
- Discuss recommendations and opportunities to advance our knowledge

Vitamin D Physiology



J Clin Invest. 2006;116(6):2062-2072

Ergocalciferol vs. Cholecalciferol

- Cholecalciferol (Vitamin D3) is the natural occurring Vitamin D in humans with exposure to sunlight.
- Ergocalciferol (vitamin D2) is made by exposing yeast/mold to UV light.
- D3 has a demonstrated a larger and more sustained effect in raising 25 vit D levels in multiple studies.

J Clin Endocrinol Metab 2011; 96(3): E447-E452

KDIGO 2009 and 2017 Update

- 3.1.3 In patients with CKD stages 3-5D, we suggest that 25(OH)D (calcidiol) levels might be measured, and repeated testing determined by baseline values and therapeutic interventions (2C). We suggest that vitamin D deficiency and insufficiency be corrected using treatment strategies recommended for the general population (2C).

- 4.2.1 In patients with CKD stages 3a-5 not on dialysis, the optimal PTH level is not known. However, we suggest that patients with levels of intact PTH progressively rising or persistently above the upper normal limit of the assay are first be evaluated for modifiable risk factors, including hyperphosphatemia, hypocalcemia, high phosphorus intake and vitamin D deficiency (2C).
- It is reasonable to correct these abnormalities with any or all of the following: reducing dietary phosphate intake and administering phosphate binders, calcium supplements, and/or native vitamin D (not graded).

• 4.2.4 In patients with CKD stage 5D requiring PTH-lowering therapy, and elevated or rising PTH we suggest calcimimetics, calcitriol, or vitamin D analogs, or calcimimetics, or a combination of calcimimetics and with calcitriol or vitamin D analogs be used to lower PTH (2B).

KDOQI Commentary

- In regards to recommendation 4.2.1 "The KDOQI work group agrees with the update and its justification especially given the high within- and between individual variability in PTH levels."
- "The updated guideline recommendation reflects the removal of the previously ungraded suggestion to consider use of phosphate binders, calcium supplements, and/or native vitamin D to address elevated PTH. Overall the KDOQI work group agrees with this change..."
- Clinical Utility "...nutritional vitamin D supplementation has increased substantially over time, likely reflecting trends in the general population."

Am J Kidney Dis. 2017;70(6):737-751

Guidelines for the General Population

- The Endocrine Society of the USA:
- 1.2 "Vitamin D deficiency is defined as a 25(OH)D below 20 ng/ml, and vitamin D insufficiency as a 25 (OH)D of 21-29 ng/ml."
- 3.0 "We suggest using either vitamin D2 or Vitamin D3 for the treatment and prevention of vitamin D deficiency."
- 3.4 "We suggest that all adults who are vitamin D deficient be treated with 50,000 IU of vitamin D2 or vitamin D3 once a week for 8 wk [or its daily equivalent] to achieve a blood level of 25(OH)D above 30 ng/ml, followed by maintenance therapy of 1500-2000 IU/d."

J Clin Endocrinol Metab. July 2011, 96(7):1911-1930

Cost of 25 Vit D Monitoring and Replacement

- Average cost of blood level around \$50 per blue cross.
- Walk-In Lab charges \$58
- Quest Lab: \$58
- Requestatest: \$59
- Replacement: Ergocalciferol 50,000 units 4 capsules: \$7-16. Average cash price: \$13.03 (GoodRx)
- OTC strengths for ergo/cholecalciferol are variable: for 5000 iu daily, 1 year supply around \$15-20

Motivations

- Widespread 25(OH)D Deficiency in CKD and ESRD
- Minimal toxicity of precursor replacement
- Inexpensive to replace (testing is a different story...)
- Possible opportunity to lower dose requirement of activated forms.
- Pleiotropic effects

Potential Pleiotropic Effects

- Beneficial Cardiovascular Effects: endothelial function, micro-circulation, arterial stiffness, blood pressure, LVH and function.
- Reduced inflammation
- Improved glucose tolerance/insulin sensitivity
- Improved acute and chronic infection rates (increased cathelicidin levels)

Other Effects

- Reduced Albuminuria with activated vit D
- Small retrospective studies have found a lower incidence of various infections with activated vit D supplementation
- Mixed results with regard to activated vit D and insulin resistance.

Recent RCTs

- Bhan et al (DIVINE) conducted a placebo-controlled, parallel-group multicenter trial comparing two doses of ergocalciferol with placebo from 10/2009 to 3/2013.
- Hemodialysis patients with 25 vit D levels < 32 were randomly assigned to weekly or monthly 50,000 i.u. ergocalciferol or placebo for a 12 week treatment period.
- End point: achievement of vitamin D sufficiency. Survival was assessed through 1 year

Clin J Am Soc Nephrol. 2015; 10: 611-619

- Vitamin D sufficiency was achieved in 91% of weekly pts, 66% of monthly pts and 35% placebo.
- Calcium, phosphate, PTH levels and active vitamin D treatment did not differ between groups.
- Hospitalizations and adverse events were similar between groups during the intervention period.
- Conclusion: Ergocalciferol can increase 25 Vit D levels in incident HD pts without alteration in serum calcium, phosphate or PTH concentrations.

Critique

- 12 weeks is not enough.
- Outcomes of interest are fracture risk, infection, cardiovascular events and overall mortality.
- The study establishes short term safety but does not answer the question of efficacy. (Vitamin D levels not withstanding)

Another RCT

- Miskulin et al. assessed the effects of supplementation with ergocalciferol on erythropoietin use and other secondary outcomes in patients on HD with vitamin D insufficiency/deficiency.
- 276 pts were randomized to 6 months of ergocalciferol or placebo.
- 25 Vit D levels increased in the ergocalciferol group, no significant change in the placebo group.

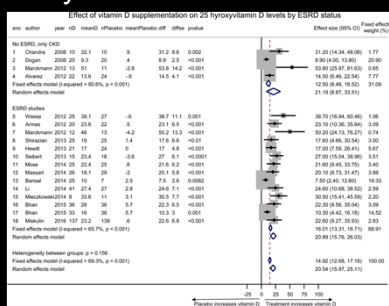
- There was no significant change in erythropoietin use between the groups and no significant difference across arms.
- No change in serum calcium, phosphorus, PTH or C-reactive protein levels.
- No change in cinacalcet, phosphate binder or calcitriol dose.
- Rates of all-cause, cardiovascular, infection related hospitalizations was not different.

Critique

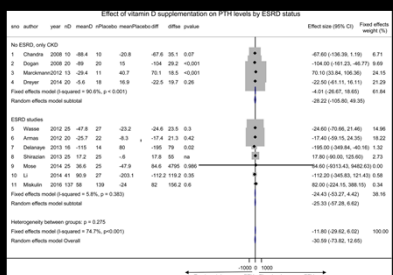
- This was not an incident population: a large percentage of these pts were already receiving CKD-MBD treatments.
- The average PTH at the start of the study was 450.
- 6 months is too short



Meta-analysis



From: Con: Nutritional vitamin D replacement in chronic kidney disease and end-stage renal disease Nephrol Dial Transplant. 2016;31(5):705-713. doi:10.1093/ndt/gfw080 Nephrol Dial Transplant | Published by Oxford University Press on behalf of ERA-EDTA 2016. This work is written by (a) US Government employee(s) and is in the public domain in the US.



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Cardiovascular Effects

- Aortic Pulse Wave Velocity and Left Ventricular Mass Index
- Mose et al. studied 64 ESRD pts
- 6 months of cholecalciferol 3000 iu daily verses placebo
- No difference in PWV and LVMI

- Hewitt et al: 60 ESRD pts.
- 50,000 iu ergocalciferol weekly for 8 weeks then monthly vs. placebo
- 6 month f/u
- No significant difference in aortic stiffness

Immune Function

- Li et al: 64 ESRD pts with 25 vit D levels < 20
- Cholecalciferol 50,000 iu weekly vs. placebo
- 12 months
- No difference in alloreactive T-cell memory as determined by IFN EISPOT

- Seibert et al: 38 ESRD pts with 25 vit D insufficiency
- Cholecalciferol 20,000 iu weekly for three months vs. placebo
- No difference in monocyte cell count, T-cell differentiation and cytokine production

- ### What to do?
- Current evidence does not support supplementation of nutritional vitamin D in dialysis patients.
 - Shortcomings in current evidence:
 - Insufficient duration of RCT
 - Lack of meaningful end points
 - Assumption that ESRD pts are the same

- It is possible that there are some dialysis patients that will benefit from chole/ergocalciferol replacement and some for whom it is futile.
- It may depend on the degree of residual kidney function, dialysis duration, exposure to other bone mineral metabolism modifying agents, comorbidities, etc.

Bibliography


Goldsmith D. Pro: Should we correct vitamin D deficiency/insufficiency in chronic kidney disease patients with inactive forms of vitamin D or just treat them with active vitamin D forms? *Neph Dial Trans* 2016; 31: 698-705.

Bhan I, et al. Nutritional Vitamin D Supplementation in Dialysis: A Randomized Trial *CJASN* 2015; 10: 611-619.

Pludowski P, et al. Vitamin D supplementation guidelines. *J Steroid Biochem Mol Biol* 2018; 175: 125-135.

Holick M, et al. Evaluation, Treatment, and Prevention of Vitamin D Deficiency: an Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab* 2011; 96(7): 1911-1930.

KDIGO 2017 Clinical Practice Guideline Update for the Diagnosis, Evaluation, Prevention, and Treatment of Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD). *Kidney International Supplements* 2017; 7: 1-59.

 University of Missouri

KDIGO Clinical Practice Guideline for the Diagnosis, Evaluation, Prevention, and Treatment of Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD). *Kidney International Supplements* 2009; 76: S1-S130.

Isakova, T. et al. KDOQI US Commentary on the 2017 KDIGO Clinical Practice Guideline Update for the Diagnosis, Evaluation, Prevention, and Treatment of Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD). *Am J Kidney Dis* 2017; 70(6): 737-751.

Parikh, C. et al. Vitamin D and Clinical Outcomes in Dialysis. *Semin Dial*. 2015; 28(6): 604-609.

Agarwal, R. et al. Con: Nutritional vitamin D replacement in chronic kidney disease and end-stage renal disease. *Nephrol Dial Transplant* 2016; 31: 706-713.

Melamed M, et al. Vitamin D Therapy in Chronic Kidney Disease and End Stage Renal Disease. *Clin J Am Soc Nephrol* 2012; 7(2): 358-365

• Pilz et al. Vitamin D Status and Mortality Risk in CKD: A Meta-analysis of Prospective Studies *AJKD*; 58(3): 374-382.
